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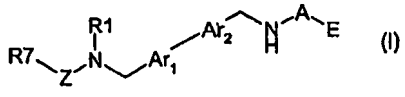
(54) Title: BIARYL COMPOUNDS HAVING ACTIVITY AT THE 5HT5A RECEPTOR



(I)

(a)

(57) Abstract: Compounds of formula (I) and pharmaceutically acceptable salts thereof are disclosed, wherein one of Ar_1 and Ar_2 is phenyl linked in a 1,4-relationship, and the other is phenyl linked in a 1,4-relationship or a 6 membered heteroaryl ring linked in a 1,4-relationship; R1 is hydrogen, or a group of formula (a), wherein X is C=O or SO_2; Y is a single bond, $-CH_2-$, $-(CH_2)_2-$, -CH=CH-, $-CH_2O-$, $-OCH_2-$, C_{3-7}cycloalkylene or NH; and R4 is optionally substituted phenyl or C_{3-7}cycloalkyl; Z is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$; R7 is NR^8R^9 where R^8 and R^9 are independently hydrogen or C_{1-6}alkyl, or R7 is optionally substituted phenyl, optionally substituted 5- or 6- membered heteroaryl ring or optionally substituted 5- or 6- membered heteroalicyclic ring; A is a single bond, $-CH_2-$, $-(CH_2)_2-$, $-CH_2CH_2O-$, or $-CH_2OCH_2-$; and E is optionally substituted phenyl, indanyl, methylenedioxyphenyl, or a 5- or 6-membered heteroaryl ring. Methods of preparation and uses thereof in medicine, for example for the treatment of CNS disorders such as depression, anxiety, sleep disorders or schizophrenia, are also disclosed.

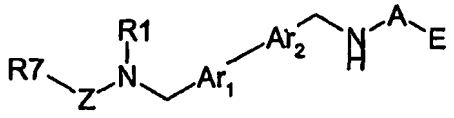
BIARYL COMPOUNDS HAVING ACTIVITY AT THE 5HT5A RECEPTOR

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and to their use in the treatment of various disorders.

The 5-HT_{5A} receptor is a receptor for 5-HT which is widely distributed in human brain (Rees *et al.*, FEBS Letters 355 242-246 [1994]). 5-HT mediates a wide range of physiological and pathological processes in the CNS. However, to date, no compounds having selective affinity at the 5-HT_{5A} receptor have been reported.

A structurally novel class of compounds have now been found that exhibit 5-HT_{5A} receptor affinity.

In a first aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:

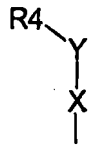


(I)

wherein

one of Ar_1 and Ar_2 is phenyl linked in a 1,4-relationship, and the other is phenyl linked in a 1,4-relationship or a 6 membered heteroaryl ring linked in a 1,4-relationship;

R1 is hydrogen, or a group of formula (a):



(a)

wherein

X is C=O or SO_2; Y is a single bond, $-CH_2-$, $-(CH_2)_2-$, $-CH=CH-$, $-CH_2O-$, $-OCH_2-$, C_{3-7}cycloalkylene or NH; and R4 is optionally substituted phenyl or optionally substituted C_{3-7}cycloalkyl;

Z is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$;

R7 is NR^8R^9 where R^8 and R^9 are independently hydrogen or C_{1-6}alkyl, or R7 is optionally substituted phenyl, optionally substituted 5- or 6- membered heteroaryl ring or optionally substituted 5- or 6- membered heteroalicyclic ring;

A is a single bond, $-CH_2-$, $-(CH_2)_2-$, $-CH_2CH_2O-$, or $-CH_2OCH_2-$; and
E is optionally substituted phenyl, optionally substituted indanyl, optionally substituted methylenedioxyphenyl, or an optionally substituted 5- or 6-membered heteroaryl ring.

R7 (when it is phenyl, 5- or 6- membered heteroaryl ring or 5- or 6- membered heteroalicyclic ring), R4 and E may be optionally substituted with 1, 2 or 3 substituents which may be the same or different and are selected from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenylC_{1-3}alkyl, CF_3, C_{1-6}alkoxy, OCF_3, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, COC_{1-6}alkyl, CO_2R^5, SO_2R^5, NR^5R^6, $CONR^5R^6$ and $SO_2NR^5R^6$ where R^5 and R^6 are independently hydrogen or C_{1-6}alkyl.

The term "halogen" and its abbreviation "halo" refer to fluorine, chlorine, bromine or iodine.

The term "C_{1-6}alkyl" refers to an alkyl group having from one to six carbon atoms, in all isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, sec-pentyl, n-pentyl, isopentyl, tert-pentyl and hexyl.

The term "C_{1-6}alkoxy" refers to a straight chain or branched chain alkoxy (or "alkyloxy") group having from one to six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, sec-pentoxy, n-pentoxy, isopentoxy, tert-pentoxy and hexoxy.

The term "C_{3-7}cycloalkyl" refers to a cycloalkyl group having from 3 to 7 carbon atoms, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.
The term "heteroaryl ring" refers to a heteroaryl ring wherein at least one atom is nitrogen, oxygen or sulfur. Examples of 5 membered heteroaryl rings include pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, isoxazolyl, oxazolyl, furazanyl, furyl and thienyl. Examples of 6 membered heteroaryl rings include pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and pyranyl.

The term "5- or 6- membered heteroalicyclic ring" refers to a heteroalicyclic ring having 5 or 6 atoms in total, at least one atom being nitrogen, oxygen or sulfur. Examples of 5 or 6 membered heteroalicyclic rings include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, dioxolanyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazinanyl, dioxanyl and dithianyl.

The term "phenylC_{1-3}alkyl" refers to benzyl, phenethyl or phenylpropyl.

The term "hydroxyC_{1-6}alkyl" refers to a C_{1-6}alkyl group substituted by a hydroxy group, such as $-CH_2OH$.

When one of Ar_1 and Ar_2 is a 6 membered heteroaryl ring, suitable examples include pyridyl, pyrimidyl and pyrazinyl. Preferably one of Ar_1 and Ar_2 is phenyl, and the other is phenyl or pyridyl.

When R7 or E is a heteroaryl ring, suitable examples include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl and pyrazinyl.

When R7 is a heteroalicyclic ring, preferably it is homopiperazine, azepine, piperidyl, piperazinyl, pyrrolidinyl or morpholinyl.

Preferably R7 is Me_2N-, 3-pyridyl, N-benzylpiperidin-4-yl, piperdin-2-yl, piperidin-3-yl, morpholinyl, 1-methylpiperazin-4-yl, 2-methylpyrazin-5-yl, 3,5-dimethylpyrazol-1-yl, methoxyphenyl, cyanophenyl or nitrophenyl.

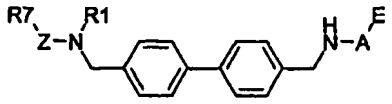
R4 can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen atom. Preferably R4 is phenyl, cyclopentyl or methylenedioxyphenyl.

Preferably Y is a single bond, $-CH_2O-$, $-(CH_2)_2-$, -CH=CH-, cyclopropyl or NH.

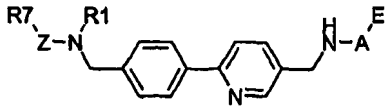
Preferably A is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_2O-$.

Preferably E is optionally substituted phenyl, optionally substituted pyridyl or methylenedioxyphenyl.

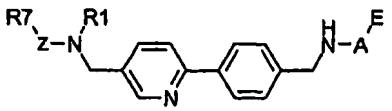
Preferred compounds are compounds of general formula (Ia), (Ib) and (Ic):



(Ia)



(Ib)



(Ic)

wherein R7, Z, R1, A and E are as defined for formula (I).

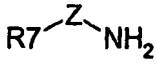
Particularly preferred compounds according to the invention are compounds E1-E41 as described below and pharmaceutically acceptable salts thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates or solvates as well as compounds containing variable amounts of water and/or solvent.

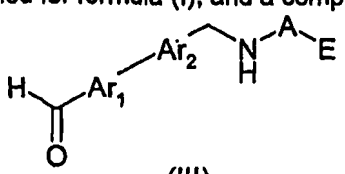
Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. geometric (or "cis-trans") isomers, diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. The present invention includes within its scope all such isomers, including mixtures.

In a further aspect, this invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II):



(II)

wherein R7 and Z are as defined for formula (I), and a compound of formula (III):



(III)

wherein Ar_1, Ar_2, A and E are as defined for formula (I), in the presence of a suitable reducing agent;

and thereafter optionally:

- removing any protecting groups, and/or
- converting a compound of formula (I) into another compound of formula (I), and/or
- forming a pharmaceutically acceptable salt.

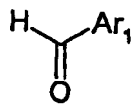
In the above process of the present invention, conditions of the reaction are as for normal reductive amination procedures. Thus, an optional dehydrating agent may be used followed by a reducing agent, such as sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as 1,2-dichloroethane, dichloromethane, THF, DMF or mixtures thereof, optionally containing methanol or acetic acid. Preferably the dehydrating agent is sodium sulfate, the reducing agent is sodium triacetoxyborohydride and the solvent is 1,2-dichloroethane containing acetic acid.

A compound of formula (I) obtained from the above process may be converted to another compound of formula (I) by standard techniques. For example, a compound of formula (I) wherein R1 is hydrogen may be converted to a compound of formula (I), wherein R1 is a group of formula (a) and X is C=O, via an acylation reaction using appropriate acid chlorides,such as cinnamyl chloride and phenoxyacetyl chloride. Similarly, a compound of formula (I) wherein R1 is hydrogen may be converted to a compound of formula (I) wherein R1 is a group of formula (a) and X is SO_2 by reacting with an appropriate sulfonyl chloride such as beta-styrylsulfonyl chloride.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. Protective groups in organic synthesis, New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, t-butyloxycarbonyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures well known in the art. For example, protecting groups such as t-butyloxycarbonyl may be removed using an acid such as hydrochloric or trifluroroacetic acid in a suitable solvent such as dichloromethane, diethylether, isopropanol or mixtures thereof.

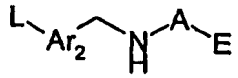
In the above process of the present invention, solid phase protection groups may also be employed, such as Wang resin, which is commercially available, optionally employing a suitable linker. Such solid phase protection groups have the advantage that work-up and purification of intermediates and products can be achieved simply by washing the support with suitable solvents.

Compounds of formula (III) may be prepared by coupling a compound of formula (IV):



(IV)

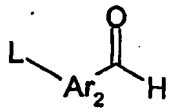
wherein Ar_1 is as defined for formula (I), and a compound of formula (V):



(V)

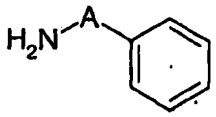
wherein Ar_2, A and E are as defined for formula (I) and L is a leaving group such as halogen, in the presence of a suitable reducing agent.

Compounds of formula (V) may be prepared by the coupling of a compound of formula (VI)



(VI)

wherein Ar_2 is as defined for formula (I) and L is a leaving group such as halogen, and a compound of formula (VII):



(VII)

wherein A is as defined for formula (I).

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The affinities of the compounds of this invention for 5-HT5A can be determined by measuring the inhibition by the compound of [3H]-LSD binding to washed cell membrane

homogenates prepared from cells stably expressing the receptor. All compounds tested according to the binding assay described above were found to have K_i values of <400nM.

The intrinsic activity of the compounds of this invention can be determined according to the [35S]GTPγS functional assay which is described in WO 99/07700.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use in the treatment of certain CNS disorders such as depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion), anxiety disorders (which includes generalised anxiety and social anxiety disorder), schizophrenia, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, pain (particularly neuropathic pain), memory disorders (including dementia, amnesic disorders and age-associated memory impairment), disorders of eating behaviours (including anorexia nervosa and bulimia nervosa), sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs (such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine and phencyclidine-like compounds, opiates such as cannabis, heroin, morphine, sedative hypnotic, amphetamine or amphetamine-related drugs such as dextroamphetamine, methylamphetamine or a combination thereof), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, and certain gastrointestinal disorders such as irritable bowel syndrome.

It is to be understood that "treatment" as used herein includes prophylaxis as well as alleviation of established symptoms.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment of a CNS disorder such as depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion), anxiety disorders (which includes generalised anxiety and social anxiety disorder), schizophrenia, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, pain (particularly neuropathic pain), memory disorders (including dementia, amnesic disorders and age-associated memory impairment), disorders of eating behaviours (including anorexia nervosa and bulimia

nervosa), sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs (such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine and phencyclidine-like compounds, opiates such as cannabis, heroin, morphine, sedative hypnotic, amphetamine or amphetamine-related drugs such as dextroamphetamine, methylamphetamine or a combination thereof), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, and certain gastrointestinal disorders such as irritable bowel syndrome. In particular the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of a CNS disorder such as depression, anxiety, sleep disorders or schizophrenia.

Compounds of the invention may be administered in combination with other active substances such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, and metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine and metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline and zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

The invention further provides a method of treatment of a CNS disorder such as depression (which term includes bipolar depression, unipolar depression, single or

recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion), anxiety disorders (which includes generalised anxiety and social anxiety disorder), schizophrenia, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, pain (particularly neuropathic pain), memory disorders (including dementia, amnesic disorders and age-associated memory impairment), disorders of eating behaviours (including anorexia nervosa and bulimia nervosa), sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs (such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine and phencyclidine-like compounds, opiates such as cannabis, heroin, morphine, sedative hypnotic, amphetamine or amphetamine-related drugs such as dextroamphetamine, methylamphetamine or a combination thereof), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, and certain gastrointestinal disorders such as irritable bowel syndrome, in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In particular, the present invention provides a method of treatment of depression, anxiety, sleep disorders or schizophrenia, in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treatment of depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion), anxiety disorders (which includes generalised anxiety and social anxiety disorder), schizophrenia, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, pain (particularly neuropathic pain), memory disorders (including dementia, amnesic disorders and age-associated memory impairment), disorders of eating behaviours (including anorexia nervosa and bulimia nervosa), sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs (such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine and phencyclidine-like compounds, opiates such as cannabis, heroin, morphine, sedative hypnotic, amphetamine or amphetamine-related drugs such as dextroamphetamine,

methylamphetamine or a combination thereof), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, and certain gastrointestinal disorders such as irritable bowel syndrome. In particular, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treatment of depression, anxiety, sleep disorders or schizophrenia.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose);, fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate);, tabletting lubricants lubricants (e.g. magnesium stearate, talc or silica);, disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants,

buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

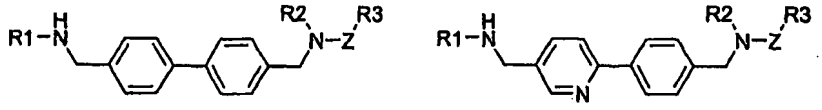
For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

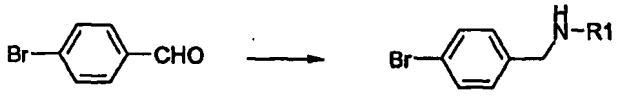
The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Preparation of compounds of the following formulae:



Z = CO, CONH, SO_2

1. Preparation of amine templates for attachment to resin

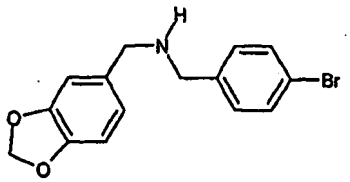


General Procedure for Reductive Amination reactions

The amine $R1NH_2$ (2 equiv.) and acetic acid (2 equiv.) were added to a stirred solution of 4-bromobenzaldehyde in anhydrous DCM. The mixture was stirred at room temperature for 45 min. after which sodium triacetoxyborohydride (1.2 equiv.) was added portionwise, allowing the effervescence to subside between additions. The reaction mixture was then stirred overnight at room temperature under argon. Sodium bicarbonate solution was added to the reaction and stirring continued until the effervescence subsided. The organic layer was separated and washed with sodium bicarbonate solution then brine. The organic layer was dried and the solvent removed *in vacuo*.

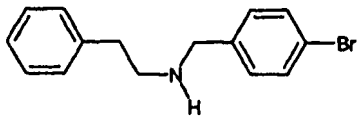
Examples:

(a) $R1NH_2$ = Piperonylamine



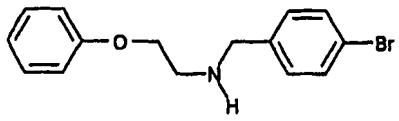
The general procedure was followed using 4-bromobenzaldehyde (13.875g, 75mmol), piperonylamine (22.65g, 18.66ml, 150mmol), acetic acid (9g, 8.58ml, 150mmol) and sodium triacetoxyborohydride (19.08g, 90mmol). The crude product was purified by flash chromatography eluting with 50% ethyl acetate/hexane to give the product as a yellow oil (19.24g, 80.1%). ^{1}H NMR ($CDCl_3$, 250MHz): δ 3.69 (2H, s), 3.73 (2H, s), 5.94 (2H, s), 6.75 (2H, s), 6.84 (1H, s), 7.21 (2H, d, J=8.3Hz), 7.44 (2H, d, J=8.3Hz). LC-MS – single peak M+H 322, 320.

b) $R1NH_2$ = Phenethylamine



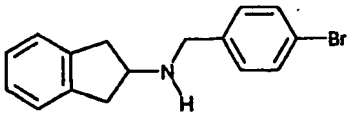
The general procedure was followed using 4-bromobenzylaldehyde (13.875g, 75mmol), phenethylamine (18.15g, 18.81ml, 150mmol), acetic acid (9g, 8.58ml, 150mmol) and sodium triacetoxyborohydride (19.08g, 90mmol). The crude product was purified by flash chromatography eluting with 50% ethyl acetate/hexane. Mass of pure compound obtained = 17.144g (78.8%). ^{1}H NMR ($CDCl_3$, 250MHz): δ 2.77-2.95 (4H, m), 3.74 (2H, s), 7.13-7.29 (7H, m), 7.38-7.47 (2H, m). LC-MS – shows a single peak, M+H 290, 292.

c) R1NH2 = 2-Phenoxyethylamine



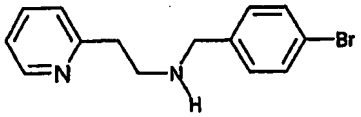
The general procedure was followed using 4-bromobenzaldehyde (3.7g), 2-phenoxyethylamine (5.48g), acetic acid (2.3 ml) and sodium triacetoxyborohydride (5.09g) in DCM (80ml). Purification of the crude product by flash chromatography (ethyl acetate-hexane 1:1) gave the the purified material (5.11g, 84%). ^{1}H NMR ($CDCl_3$, 250MHz): δ 3.00 (2H, t), 3.83 (2H, s), 4.09 (2H, t), 6.88-6.98 (3H, m), 7.22-7.31(4H, m) and 7.45 (2H, m). LC-MS shows a single peak, M+H 306, 308.

d) R1NH2 = 2-aminoindan



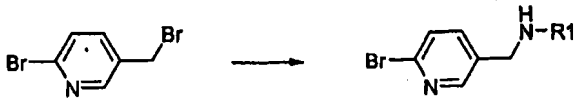
The general procedure was followed using 4-bromobenzaldehyde (3.7g), 2-aminoindan (5.00g), acetic acid (2.3 ml) and sodium triacetoxyborohydride (5.09g) in DCM (80ml). Purification of the crude product by flash chromatography (ethyl acetate-hexane 2:3) gave the the purified material (5.16g, 85%). ^{1}H NMR ($CDCl_3$, 250MHz): δ 2.79 (2H, dd), 3.17 (2H, dd), 3.65 (1H, m), 3.81 (2H, s), 7.10-7.25 (6H,m) and 7.44 (2H,m). LC-MS shows a single peak, M+H 302, 304.

e) R1NH2 = 2-(2-aminoethyl)pyridine



The general procedure was followed using 4-bromobenzaldehyde (3.7g), 2-(2-aminoethyl)pyridine (4.88g), acetic acid (2.3 ml) and sodium triacetoxyborohydride (5.09g) in DCM (80ml). Purification of the crude product by flash chromatography (5% methanol in DCM) gave the the purified material (4.34g, 75%). ^{1}H NMR ($CDCl_3$, 250MHz): δ 3.01 (4H, m), 3.77 (2H, s), 7.09-7.19 (4H, m), 7.41 (2H, m), 7.59 (1H, dt), 8.53 (1H, d). LC-MS shows a single peak, M+H 291, 293.

General Procedure for Alkylation Reactions



A solution of the amine (1 equiv) and 2-bromo-5-bromomethylpyridine [Windscheif, P-M.; Voegtle, F.; Synthesis 1994; 87-92] in DMF were stirred at room temperature for 15h. The solvent was removed under vacuum and the residue purified by silica gel chromatography.

Examples

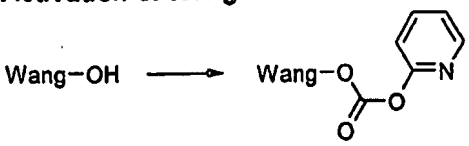
a) R1 = phenethyl

The general procedure was followed using 2-bromo-5-bromomethylpyridine (8.7 g) and phenylethylamine (16.7 g) in DMF (250 ml). Silica gel chromatography (4% MeOH in DCM) gave the pure product (10.0 g, 99%). ^{1}H NMR ($CDCl_3$, 400MHz): δ 2.77-2.90 (4H,

m), 3.76 (2H, s), 7.18-7.32 (5H, m), 7.45 (1H, d), 7.52 (1H, dd), 8.27 (1H, d). LC-MS – shows a single peak, M+H 291, 293.

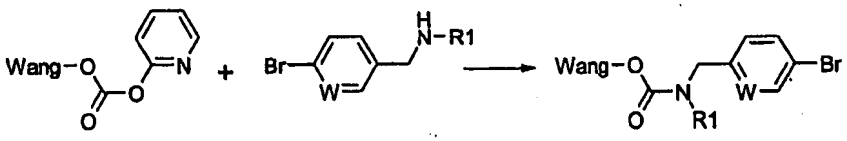
2. Attachment of Amine Templates to Wang Resin.

Activation of Wang Resin



Wang resin (15.88g, 1.7mmol.g^{-1}, 27mmol) was suspended in anhydrous DCM and di-2-pyridylcarbonate and triethylamine were added. The mixture was shaken overnight under argon. The resin was filtered and washed 4 times with DCM then dried at room temperature in vacuo and used without further characterisation..

General Procedure for Attachment of Amine Templates



The resin was suspended in anhydrous DCM and the amine (2 equiv.) added. The suspension was then shaken under argon at room temperature for 24h. The resin was then filtered, washed with DCM, THF(x3) and DCM (x3) then dried *in vacuo* at 40°C.

Examples

(a) R1 = Phenethyl, W = CH

The general procedure was followed using 2-pyridyl carbonate resin (5.56g, 7.4 mmol) and N-phenethyl-4-bromobenzylamine (4.29g, 14.8 mmol)) in anhydrous DCM (80ml). Mass of resin obtained = 6.58g. A small sample was cleaved in 20% TFA/DCM for 2h. ^{1}H NMR (250MHz, CD_3OD): δ 2.96-3.06 (2H, m), 3.22-3.33 (2H, m), 4.21 (2H, s), 7.21-7.43 (7H, m), 7.60-7.69 (2H, m).

(b) R1 = 3,4-Methylenedioxybenzyl, W = CH

The general procedure was followed using 2-pyridyl carbonate resin (19g, 26.8mmol). and N-(3,4-methylenedioxybenzyl)-4-bromobenzylamine (17.3g, 54 mmol). Mass of resin obtained = 25.03g. A small sample was cleaved in 20% TFA/DCM for 2h. ^{1}H NMR

(250MHz, CD_3OD): δ 4.15 (2H, s), 4.19 (2H, s), 6.00 (2H, s), 6.86-6.97 (3H, m), 7.39 (2H, d, J=8.6Hz), 7.63 (2H, d, J=8.6Hz).

(c) R1 = 2-Phenoxyethyl, W = CH

The general procedure was followed using 2-pyridyl carbonate resin (5.56g, 7.4 mmol) and N-(2-phenoxyethyl)-4-bromobenzylamine (4.53g, 14.8mmol) in DCM (80ml). Mass of resin obtained = 6.71g. A small sample was cleaved in 20% TFA/DCM for 2h. ^1H NMR (250MHz, CD_3OD): δ 3.39 (2H, τ, J = 5.0Hz), 4.18 (2H, t, J=5.0Hz), 4.21 (2H, s), 6.90 (3H, m), 7.22 (2H, m), 7.35 (2H, m) and 7.55 (2H, m).

(d) R1 = Indan-2-yl, W = CH

2-Pyridyl carbonate resin (5.56g, 7.4mmol) was suspended in dry 1,2-dichloroethane (70ml) in a glass tube. N-(indan-2-yl)-4-bromobenzylamine (4.47g, 14.8mmol) was added to the mixture and the tube was then rotated in an oven at 50°C for 27h. The mixture was cooled and the resin was filtered and washed with DCM (x3), THF (x3) and DCM (x3), before drying in vacuo at 40 °C Mass of product resin = 6.75g. A small quantity of resin was cleaved with 20% TFA/DCM for 2h. ^1H NMR (250MHz, CD_3OD): δ 3.17 (2H, δd), 3.50 (2H, dd), 4.11 (1H, m), 4.27 (2H, s), 7.24 (4H, m), 7.45 (2H, m) and 7.64 (2H, m).

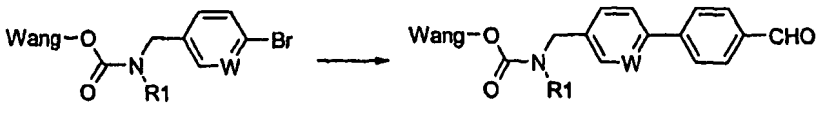
(e) R1 = 2-(2-Pyridyl)ethyl, W = CH

The general procedure was followed using 2-pyridyl carbonate resin (5.56g, 7.4 mmol) and N-[2-(2-pyridyl)ethyl]-4-bromobenzylamine (4.31g, 14.8mmol) in DCM (80ml). Mass of resin obtained = 6.61g. A small quantity of resin was cleaved with 20% TFA/DCM for 2h. ^1H NMR (250MHz, CD_3OD): δ3.28 (2H, μ), 3.47 (2H, m), 4.27 (2H, s), 7.40-7.53 (4H, m), 7.63 (2H, m), 7.99 (1H, m) and 8.59 (1H, m).

(f) R1 = Phenethyl, W = N

The general procedure was followed using 2-pyridyl carbonate resin and (6-Bromo-pyridin-3-ylmethyl)-phenethylamine in anhydrous DCM (80ml). Mass of resin obtained = g. A small sample was cleaved in 20% TFA/DCM for 2h. LC-MS – shows a single peak, M+H 291, 293. ^1H NMR (400MHz, CD_3OD): δ 3.02 (2H, dd), 3.32 (2H, dd), 4.28 (2H, s), 7.26-7.37 (5H, m), 7.72 (1H, d), 7.82 (1H, dd), 8.47 (1H, d).

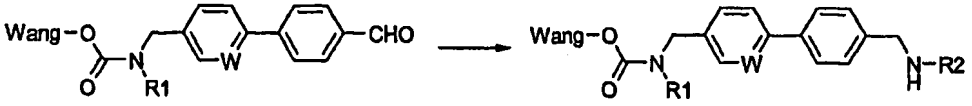
3. Procedure for Solid Phase Suzuki Reaction.



W = CH, N

Resins were loaded into IRORI microkans (0.035mmol.kan^{-1}) containing a radiofrequency tag, and the kans were suspended in DME (1ml per kan) in a 3-necked flask. Vacuum was applied and released several times to ensure that the kans were properly filled with solvent. The flask was fitted with an overhead stirrer, condensor and thermometer then purged with argon for 1.5 hours. Fresh $Pd(PPh_3)_4$ (0.15 equiv.) was added followed by 4-formylbenzeneboronic acid (3 equiv.) after about five minutes. Sodium carbonate (6 equiv.) in water (DME:water ratio 9:1) was added and the mixture was heated until gentle reflux was obtained (internal temp. ~75°C). The mixture was stirrred under reflux in an argon atmosphere for 18h and the reaction then allowed to cool. The reaction solution was decanted and the kans rinsed with THF-water (1:1 x2), water (x3) and THF-water. They were then transferred to a kan washer and washed with THF, THF-water (1:1 x2), water (x2), THF (x3) and DCM (x3). The kans containing resin product were then dried overnight *in vacuo* at 40°C.

4. Solid Phase Reductive Amination Reactions



General conditions for solid phase reductive aminations reactions.

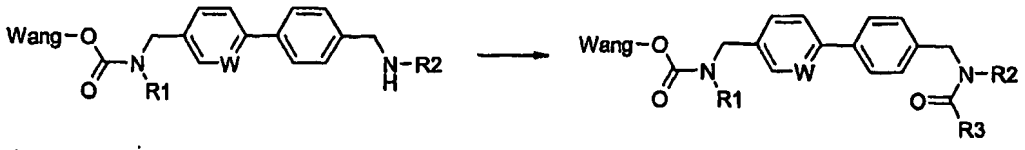
W = CH, N

Kans containing the resin-bound biphenyl aldehydes (0.035mmol per kan), Na_2SO_4 (5 equiv.) and 1,2-dichoroethane (DCE) (1ml per kan) were placed into flasks and vacuum applied and released. The amine $R2NH_2$ (5 equiv.) was added as a solution in DCE (~8mmol/ml) followed by acetic acid (5 equiv.). The mixture was shaken under argon for 3 hours before adding solid sodium triacetoxyborohydride (4 equiv.). The mixture was then shaken for a further 24 hours under argon. The reaction mixture was decanted and the kans rinsed with DCM (x3), THF, THF-H_2O (1:1), H_2O and THF-H_2O (1:1). They were then transferred to a kan washer and washed with THF, THF-H_2O (1:1), H_2O(x2), THF-H_2O (1:1), THF, DMF, THF (x3) and DCM (x3). The kans containing resin product were dried *in vacuo* at 40°C.

Examples of amines used are: N-(2-aminoethyl)morpholine, 3-(aminomethyl)pyridine, 4-amino-1-benzylpiperidine, N,N-dimethylethylenediamine, 3-methoxyphenethylamine, 3-phenylpropylamine,
1-(3-aminopropyl)-4-methylpiperazine, 2-(aminomethyl)pyridine, 5-methyl-2-(aminomethyl)pyrazine, 3-amino-1-BOC-piperidine, 2-(aminomethyl)-1-BOC-piperidine and 3-(dimethylamino)propylamine.

5. Further Reactions of Resin Bound Secondary Amines

(a) *General procedure for acylation reactions with acid chlorides*



W = CH, N

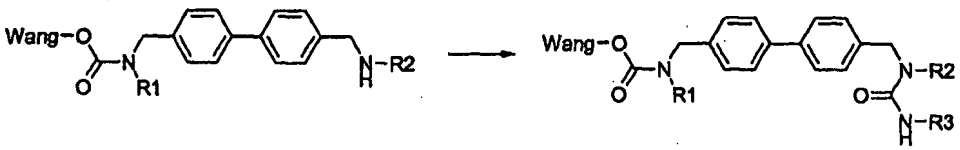
Kans containing the resin-bound secondary amines (0.035mmol per kan) were placed in a flask with DCM (1ml per kan) and vacuum applied and released. Triethylamine was added (12 equiv.) followed by the acid chloride (10 equiv.) dissolved in a little DCM. The reaction was placed under argon and shaken at room temperature for 18h.

The reagent solution was removed from the flask and the kans rinsed with DCM (x3). They were then washed in a kan washer with DCM (x2), THF (x3) and DCM (x3). The kans containing resin product were then dried overnight *in vacuo* at 40°C.

Examples of acid chlorides used are;

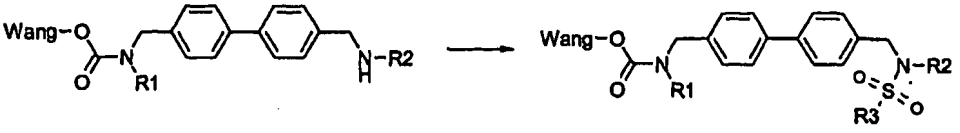
Cinnamoyl chloride, thiophene-2-carbonyl chloride 3,4-methylenedioxybenzoyl chloride, 3-phenylpropionyl chloride, *trans*-2-phenylcyclopropanecarbonyl chloride, cyclopentylacetyl chloride and phenoxyacetyl chloride.

(b) *General procedure for reactions with isocyanates*



The general procedure for acid chlorides applies except that triethylamine was omitted. An example of an isocyanate used is phenyl isocyanate (R3 = NHPh)

(c) *General procedure for reaction with sulfonyl chlorides*

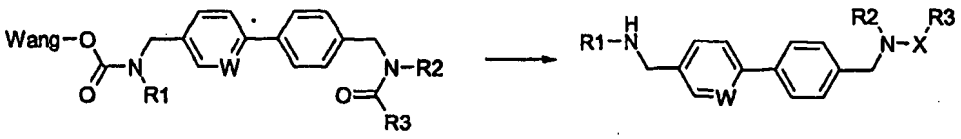


The general procedure for acid chlorides applies except that triethylamine was replaced with pyridine (11 equivalents) and 4-dimethylaminopyridine (1 equivalent).

An example of a sulfonyl chloride used is is beta-styrylsulfonyl chloride.

(d) General procedure for reaction with carboxylic acids

6. Cleavage of Final Products from the Resin

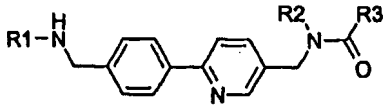


W = CH, N; X = CO, CONH, SO_2

The kans containing resin-bound products were arrayed into cleavage plates and treated with 2ml of 20% TFA/DCM for 2 hours. The solutions were filtered into preweighed vials and the kans washed with a further 1ml DCM. The solvent was removed in vacuo at 40°C to afford the cleaved products. This procedure also removes any N-BOC protecting groups.

Products were analysed by LC/MS and if necessary purified using high throughput preparative HPLC.

Preparation of compounds of the following formula:



1. Solution Phase Alkylation Reactions

General Procedure for Alkylation Reactions

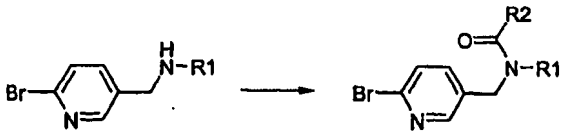
A solution of the amine (1 equiv) and 2-bromo-5-bromomethylpyridine [Windscheif, P-M.; Voegtle, F.; Synthesis 1994; 87-92] in DMF were stirred at room temperature for 15h. The solvent was removed under vacuum and the residue purified by silica gel chromatography.

Examples

a) R1 = dimethylaminoethyl

The general procedure was followed using 2-bromo-5-bromomethylpyridine (3.9 g) and dimethylamino ethylamine (5.5 g) in DMF (100 ml). Silica gel chromatography (4% MeOH in DCM) gave the pure product (0.62 g, 25%). LC-MS – shows a single peak, M+H .

2. Solution Phase Acylation Reactions



General procedure for acylation reactions with acid chlorides

A solution of the amine in DCM was treated with pyridine followed by the acid chloride, stirred at room temperature for 3h, diluted with DCM, washed with sat. aq. $NaHCO_3$ and dried over $MgSO_4$. Concentration to dryness under vacuum gave the desired product.

Examples

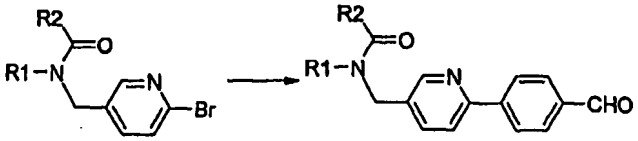
a) R1 = dimethylaminoethyl, R2 = cyclopentylethyl

The general procedure was followed using *N'*-(6-Bromo-pyridin-3-ylmethyl)-*N,N*-dimethyl-ethane-1,2-diamine (200 mg), 3-cyclopentylpropionyl chloride (138 mg), pyridine (0.13 ml) and DCM (10 ml). Preparative HPLC gave the desired product (253 mg, 85%).

b) R1 = dimethylaminoethyl, R2 = phenylethenyl

The general procedure was followed using *N'*-(6-Bromo-pyridin-3-ylmethyl)-*N,N*-dimethyl-ethane-1,2-diamine (200 mg), cinnamoyl chloride (143 mg), pyridine (0.13 ml) and DCM (10 ml). Preparative HPLC gave the desired product (247 mg, 82%).

3. Solution Phase Suzuki Reactions



General Procedure for Suzuki Coupling Reactions

A stirred solution of the bromopyridine in DME was treated with 4-formylboronic acid and a solution of Na_2CO_3 in water. The mixture was degassed with argon for 30 mins then

treated with fresh $Pd(PPh_3)_4$ and heated at 80 for 20h. The solvent was removed under vacuum and the residue partitioned between DCM and sat. aq. Na_2CO_3. The organic layer was dried over MgSO4, filtered and concentrated to dryness under vacuum.

Examples

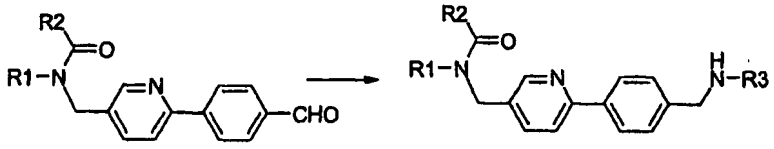
a) R1 = dimethylaminoethyl, R2 = cyclopentylethyl

The general procedure was followed using *N'*-(6-Bromo-pyridin-3-ylmethyl)-*N'*-(3-cyclopentylpropionyl)-*N,N*-dimethyl-ethane-1,2-diamine (110 mg), 4-formylboronic acid (47 mg), $Pd(PPh_3)_4$ (17 mg), Na_2CO_3 (92 mg), water (2.5 ml) and DME (7.5 ml). The crude product was purified using HPLC (5% MeOH in DCM) giving the desired product (72 mg, 61%).

b) R1 = dimethylaminoethyl, R2 = phenylethenyl

The general procedure was followed using *N'*-(6-Bromo-pyridin-3-ylmethyl)-*N'*-(3-cyclopentylpropionyl)-*N,N*-dimethyl-ethane-1,2-diamine (240 mg), 4-formylboronic acid (165 mg), $Pd(PPh_3)_4$ (36 mg), Na_2CO_3 (200 mg), water (2.5 ml) and DME (7.5 ml). The crude product was purified using HPLC (5% MeOH in DCM) giving the desired product (140 mg, 55%).

4. Solution Phase Reductive Amination Reactions



General procedure for solution phase reductive amination reactions

A stirred solution of the aldehyde in DCM was treated with the amine followed by acetic acid. The mixture was stirred for 30 mins under argon and then treated with sodium triacetoxyborohydride, and stirred for a further 16 h. The mixture was diluted with DCM and washed with sat. aq. Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness under vacuum.

Examples

a) R1 = dimethylaminoethyl, R2 = cyclopentylethyl, R3 = phenethyl

The general procedure was followed using 3-cyclopentyl-N-(2-dimethylamino-ethyl)-N-[6-(4-formyl-phenyl)-pyridin-3-ylmethyl]-propionamide (65 mg), phenethylamine (22 mg),

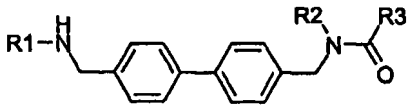
acetic acid (19 mg), sodium triacetoxyborohydride (68 mg), and DCM (10 ml). The residue was purified using HPLC giving the desired product (55 mg, 67%).

b) R1 = dimethylaminoethyl, R2 = phenylethenyl, R3 = phenethyl

The general procedure was followed using (E)-N-(2-Dimethylamino-ethyl)-N-[6-(4-formyl-phenyl)-pyridin-3-ylmethyl]-3-phenyl-acrylamide (140 mg), phenethylamine (50 mg), acetic acid (40 mg), sodium triacetoxyborohydride (144 mg), and DCM (10 ml). The residue was purified using HPLC giving the desired product (7 mg, 4%).

Examples

The following compounds, synthesized by the above methodology, were found to be 5-HT5A antagonists with Ki <400 nM.



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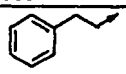
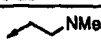
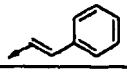
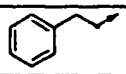
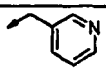
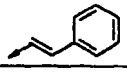
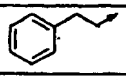
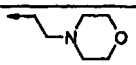
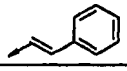
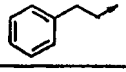
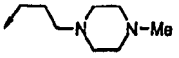
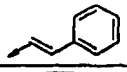
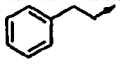
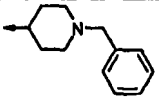
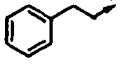
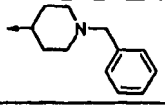
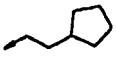
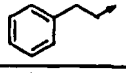
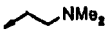
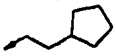
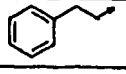
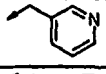
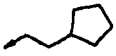
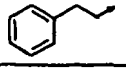
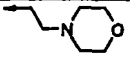
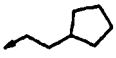
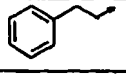
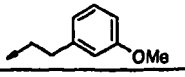
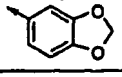
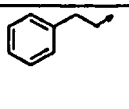
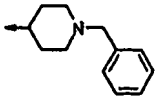
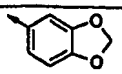
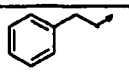
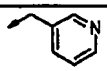
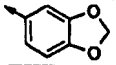
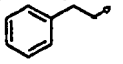
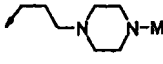
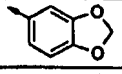
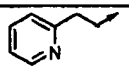
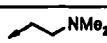
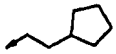
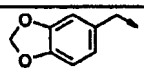
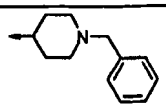
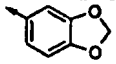
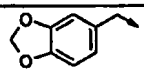
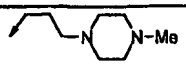
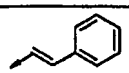
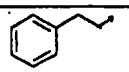
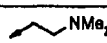
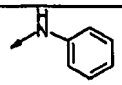
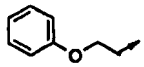
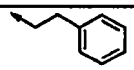
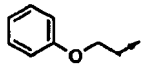
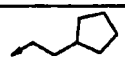
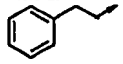
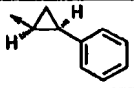
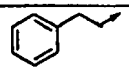
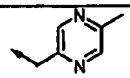
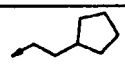
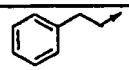
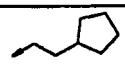
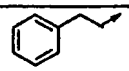
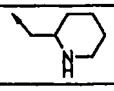
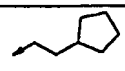
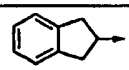
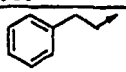
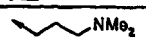
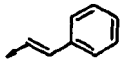
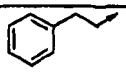
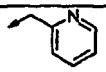
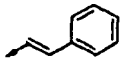
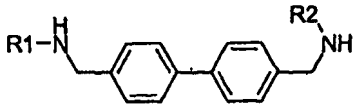
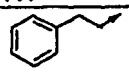
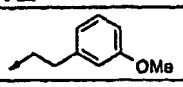
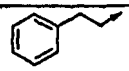
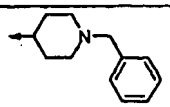
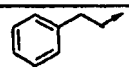
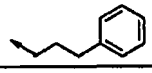
E1				517
E2				537
E3				559
E4				586
E5				593
E6				613
E7				511
E8				531
E9				553
E10				598

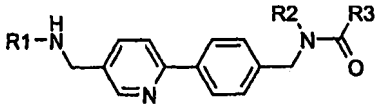
E11				637
E12				555
E13				604
E14				512
E15				667
E16				616
E17				506
E18				535
E19				527
E20				531
E21				546
E22				523
E23				537
E24				523
E25				509
E26				521
E27				541

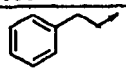
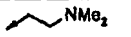
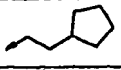
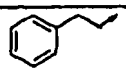
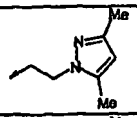
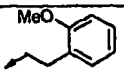
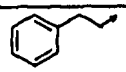
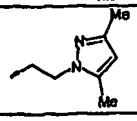
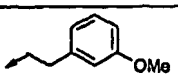
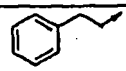
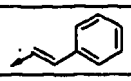
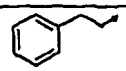
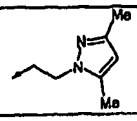
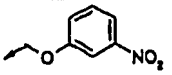
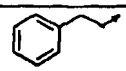
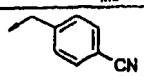
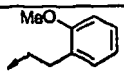
5

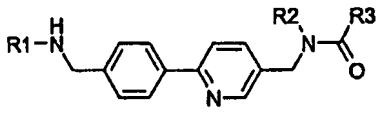
No.	R1	R2	R3	M
E28				567
E29				573

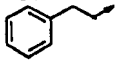
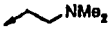
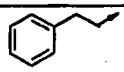
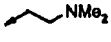
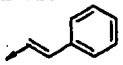


No.	R1	R2	M
E30			450
E31			489
E32			434



No.	R1	R2	R3	M
E33				512
E34				602
E35				602
E36				518
E37				619
E38				595

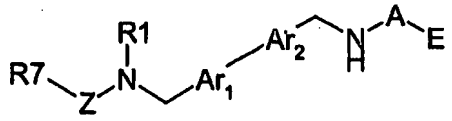


No.	R1	R2	R3	M
E39				512
E40				518

Each compound was analysed by LCMS (215 nm) and consisted of a single peak with the expected MH^+ ion corresponding to the mass listed.

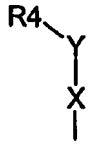
CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof: pharmaceutically acceptable salt thereof:



(I)

wherein
one of Ar_1 and Ar_2 is phenyl linked in a 1,4-relationship, and the other is phenyl linked in a 1,4-relationship or a 6 membered heteroaryl ring linked in a 1,4-relationship;
R1 is hydrogen, or a group of formula (a):



(a)

wherein
X is C=O or SO_2; Y is a single bond, $-CH_2-$, $-(CH_2)_2-$, -CH=CH-, $-CH_2O-$, $-OCH_2-$, C_{3-7}cycloalkylene or NH; and R4 is optionally substituted phenyl or C_{3-7}cycloalkyl;

Z is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$;
R7 is NR^8R^9 where R^8 and R^9 are independently hydrogen or C_{1-6}alkyl, or R7 is optionally substituted phenyl, optionally substituted 5- or 6- membered heteroaryl ring or optionally substituted 5- or 6- membered heteroallcyclic ring;
A is a single bond, $-CH_2-$, $-(CH_2)_2-$, $-CH_2CH_2O-$, or $-CH_2OCH_2-$; and
E is optionally substituted phenyl, indanyl, methylenedioxyphenyl, or a 5- or 6-membered heteroaryl ring.

2. A compound as claimed in claim 1, wherein R7 is Me_2N-, 3-pyridyl, N-benzylpiperidin-4-yl, piperdin-2-yl, piperidin-3-yl, morpholinyl, 1-methylpiperazin-4-yl, 2-methylpyrazin-5-yl, 3,5-dimethylpyrazol-1-yl, methoxyphenyl, cyanophenyl or nitrophenyl.

3. A compound as claimed in claim 1 or claim 2, wherein one of Ar_1 and Ar_2 is phenyl linked in a 1,4-relationship, and the other is phenyl linked in a 1,4-relationship or pyridyl linked in a 1,4-relationship.

4. A compound as claimed in claim 1, 2 or 3, wherein R4 is phenyl, cyclopentyl or methylenedioxyphenyl.

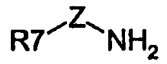
5. A compound as claimed in any of claims 1-4, wherein Y is a bond, $-CH_2O-$, $-OCH_2-$, $-(CH_2)_2-$, -CH=CH-, cyclopropyl or NH.

6. A compound as claimed in any of claims 1-5, wherein A is a bond, CH_2, $(CH_2)_2$ or $(CH_2)_2O$.

7. A compound as claimed in any of claims 1-6, wherein E is phenyl, pyridyl or methylenedioxyphenyl.

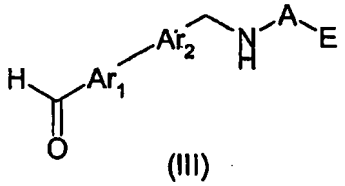
8. A compound as claimed in claim 1 which is any of E1-E40 or a pharmaceutically acceptable salt thereof.

9. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II):



(II)

wherein R7 and Z are as defined for formula (I), and a compound of formula (III):



(III)

wherein Ar_1, Ar_2, A and E are as defined for formula (I), in the presence of a suitable reducing agent;

and thereafter optionally:

- removing any protecting groups, and/or
- converting a compound of formula (I) into another compound of formula (I), and/or
- forming a pharmaceutically acceptable salt.

10. A compound as claimed in any of claims 1-8 or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance.

11. A compound as claimed in any of claims 1-8 or a pharmaceutically acceptable salt thereof for use in the treatment of a CNS disorder.

12. A compound as claimed in claim 11 wherein the disorder is depression, anxiety, a sleep disorder or schizophrenia.

13. A method of treatment of a CNS disorder in a mammal including human, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound as claimed in any of claims 1-8 or a pharmaceutically acceptable salt thereof.

14. A method as claimed in claim 13 wherein the disorder is depression, anxiety, a sleep disorder or schizophrenia.

15. Use of a compound as claimed in any of claims 1-8 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treatment of a CNS disorder.

16. The use as claimed in claim 15, wherein the disorder is depression, anxiety, a sleep disorder or schizophrenia.

17. A pharmaceutical composition, which comprises a compound as claimed in any of claims 1-8 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

18. A process for preparing a pharmaceutical composition as defined in claim 17, comprising mixing a compound as defined in any of claims 1-8 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004658

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/40 C07D295/12 C07D211/58 C07D317/50 C07D405/12
C07D405/14 C07D241/12 C07D211/56 C07D213/38 C07D401/12
C07C233/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2002, XP002291510 Database accession no. 2002:539647 443340-86-1, 443340-87-2, 443340-88-3, 443340-89-4, 443340-90-7 & WO 02/055484 A (ISHIKAWA EIICHIRO ; KORI MASAKUNI (JP); NAKATA MIKIYO (JP); KOBAYASHI) 18 July 2002 (2002-07-18)	1-7, 10-12, 17,18
E	WO 2004/035521 A (PREUSS ANDREA ; BRUNNER FREDERIC (CH); CIBA SC HOLDING AG (CH); MEHLIN) 29 April 2004 (2004-04-29) page 9; compounds 15,17 page 10; compound 20 claim 1	1-7, 10-12, 17,18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2004	19/08/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004658

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 276 161 A (GLAXO GROUP LTD) 21 September 1994 (1994-09-21) the whole document	1-18
A	WO 02/060875 A (CHAMBERS ROBERT JAMES ; MAGEE THOMAS VICTOR (US); MARFAT ANTHONY (US);) 8 August 2002 (2002-08-08) pages 109-112; claim 2	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/004658

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 2003055326 A	26-02-2003
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		CA 2436535 A1	08-08-2002
		EE 200300360 A	15-12-2003
		EP 1355884 A1	29-10-2003
		HU 0400637 A2	28-06-2004
		WO 02060875 A1	08-08-2002
		NO 20033397 A	19-09-2003
		US 2002193612 A1	19-12-2002
		US 2004048903 A1	11-03-2004